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SHORT REPORT

Association of Invasive Breast Carcinoma and Glioblastoma Multiforme: a Case Report with Histological and Immunohistochemical Features

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Breast cancer is the most common cancer (21%) and the second leading cause of cancer deaths among women. Annual breast cancer deaths are exceeded only by those from lung cancer (1). In contrast, brain tumors are relatively rare and are found at autopsy with a frequency of between 1 and 2% (2). Half of the newly discovered brain tumors each year are metastatic lesions, and breast cancer appears to be the second leading cause of brain metastasis (3). On the other hand, neuroepithelial tumors account for 50 to 60% of primary intracranial tumors in adults, and glioblastoma multiforme constitutes 50% of them (4).

We report here the association between breast and brain cancers in a 46 year-old woman. An association between these 2 frequent neoplasms is possible, especially in the rare autosomal dominant Li-Fraumeni syndrome, but otherwise such an association is rare. Since we were unable to obtain any hereditary or extrinsic factors from the patient's history, we decided to investigate some oncogenic and hormone receptor proteins, which could later be taken into consideration when explaining the pathogenesis of 2 associated malignancies.

Case report

A 46 year-old female who had underwent a modified radical mastectomy procedure one month previously was admitted to our neurosurgery department with complaints of severe headache and vomiting that had progressed within the previous 3 days. Her neurological examination was normal except for the finding of papilledema on fundoscopy. Her breast cancer was histologically diagnosed as micropapillary carcinoma (Figure 1). Her history did not reveal any other family member affected by a cancer. After a month, a left frontal cystic tumor with a mural nodule that was enhanced with the administration of contrast material was seen on computerized tomographic scanning. Since the histopathologic diagnosis after the previous mastectomy procedure which was performed one month ago was invasive micropapillary adenocarcinoma, the left frontal lesion was expected to be metastasis. Magnetic resonance was also performed to disclose any other lesion that would support the diagnosis of a metastatic disease, but it was a single enhancing cysctic lesion with an irregular shaped mural nodule, and surrounding edema.

A gross total removal of the tumor was accomplished via a left frontal craniotomy. The tumor was fragile and

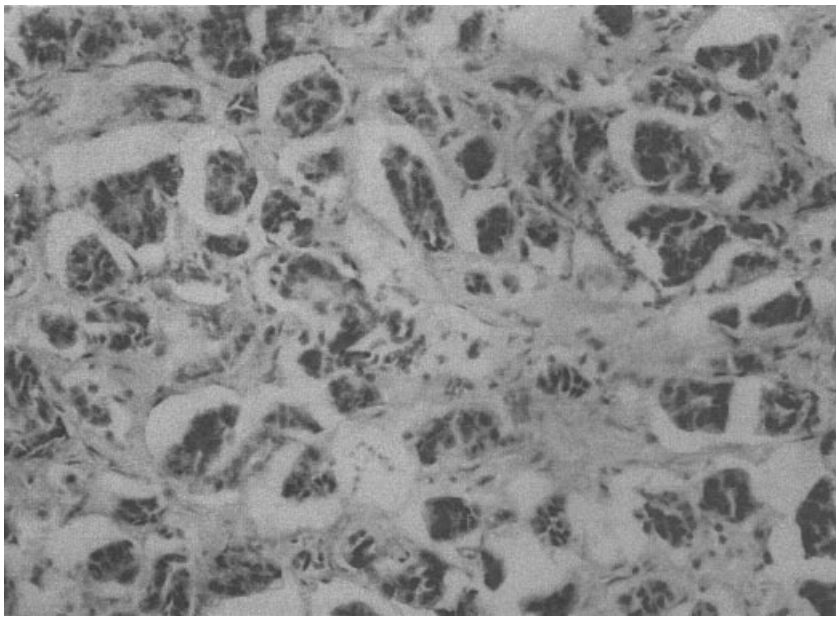

Figure 1. Histological appearance of micropapillary carcinoma in the breast. H+E staining, X100.

had a purple-grayish color. The postoperative course was smooth and the patient remained neurologically intact. No other possible metastatic lesion could be determined during a detailed survey of the systems. The histopathologic diagnosis was glioblastoma multiforme (Figure 2). Immunohistochemically, tumor cells showed glial fibrillary acidic protein positivity (Figure 3), but cytokeratin was negative.

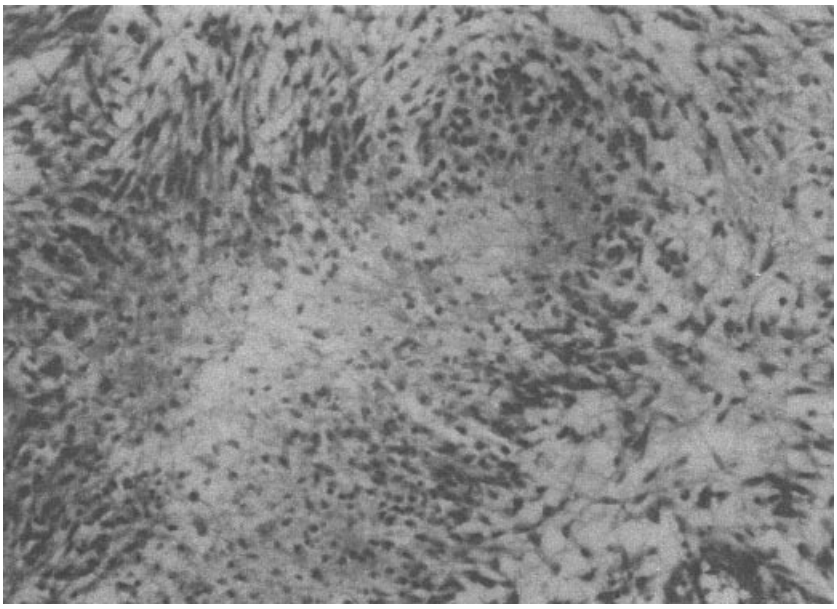

Figure 2. Histological appearance of glioblastoma cells. Note the palisading tumor cells around the necrosis. H+E staining, X100.

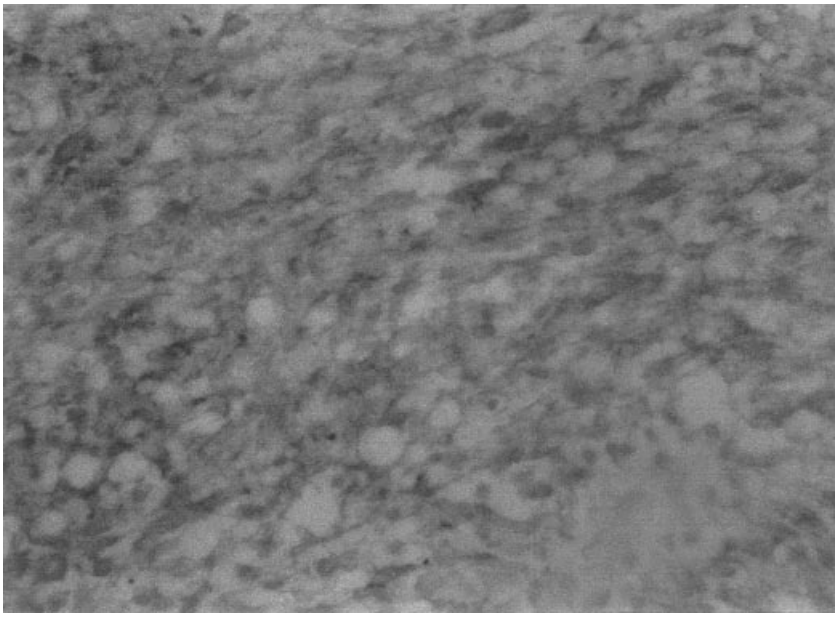

Figure 3. Cytoplasmic glial fibrillary acidic protein positivity in glioblastoma cells. Immunoperoxidase staining, X100.

The breast cancer council of our hospital decided to treat patient with postoperative radiotherapy and oral doses of tamoxifen. The patient began to use tamoxifen at a daily oral dose of 20 mg and underwent a whole brain radiation of 6000 cGy. The patient was discharged and continued the oral use of tamoxifen and phenytoin. Her latest examination was performed in the fifth postoperative month and she was still neurologically intact with no evidence of recurrence on computerized tomography, or metastasis.

We studied estrogen and progesterone receptor activity in addition to c-erbB2 and p53 protein expression, in both tumors using immunohistochemistry. The invasive micropapillary carcinoma showed positivity for progesterone (Figure 4) and p53 protein, whereas the immunohistochemical staining for estrogen and c-erbB2 was negative. The tumor cells in the glioblastoma multiforme case were negative for all of the immunohistochemical markers (Table).

The pathogenesis of multiple primary neoplasms is unknown. While extrinsic factors such as environmental effects including irradiation or chemical exposure to the host genome might be important for heterochronous multiple primary neoplasms, intrinsic factors, age, immunity or genetic factors (for example, the rare autosomal dominant Li-Fraumeni syndrome) have been proposed as possible mechanisms in the occurrence of multiple primary neoplasms (5,6).

Overexpression or amplification of various oncogenes has been widely studied in either breast cancer or gliomas previously. Of these, germline p53 mutations were found to be correlated with an increased risk of developing breast cancer, brain tumor, osteosarcoma, leukemia and adrenocortical carcinomas (7). Overall, approximately 50% or more of astrocytoma (8) and 40% of breast cancer specimens evaluated by immunohistochemistry stained positively for p53 (9), regardless of the histological grade. In addition, a higher frequency of c-erbB2 immunoreactivity was observed in anaplastic astrocytomas (81.8%) and glioblastomas (62.5%) than in low grade astrocytomas (10). C-erbB2 immunoreactivity was frequently investigated in breast cancer patients and was found to be positive in about 40% of patients (9). We studied both c-erbB2 and p53 protein expressions in both pathologic specimens of our patients, and found that the tumor cells in breast cancer were positive for p53, while they were negative in glioblastoma multiforme. This finding suggested that the brain tumor was a primary (de novo) subtype of glioblastoma multiforme rather than a secondary subtype progressing from a low-grade or anaplastic astrocytoma.

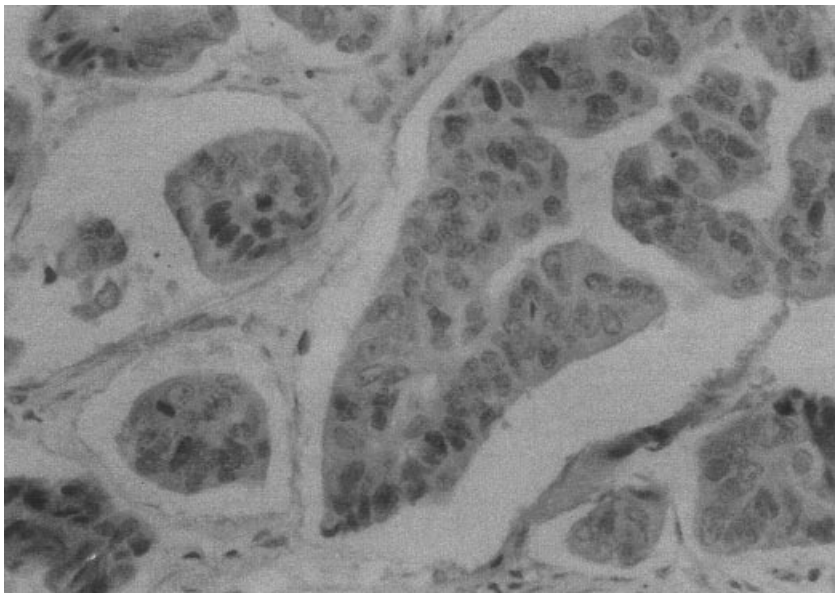

Figure 4. Nuclear progesterone receptor protein positivity in breast cancer cells. Immunoperoxidase staining, X100.

Table. The results of the immunoreactivity of the breast cancer and glioblastoma multiforme case for estrogen receptor, progesterone receptor, p53 and c-erbB-2 oncogenes.

	Estrogen receptor,	Progesterone receptor	p53	c-erbB-2 .
Breast cancer (4805/00)	-	+	+	- .
Glioblastoma multiforme (6713/00)	-	-	-	- .

The relation ship between sex steroid receptors and the pathogenesis and/or treatment of either breast cancer and prostatic carcinoma has previously been shown, and so in recent years (11), there has been increasing interest in the role of these receptors in brain tumors. Progesterone receptors in astrocytic tumors were found to correlate with histologic grade and to participate in the growth of these tumors and tumor angiogenesis (12). Androgen and glucocorticoid receptor mRNAs were detected in all astrocytic neoplasms. Progesterone receptor mRNA was observed more frequently in high-grade gliomas than in low-grade gliomas (13). Normal astrocytes were consistently negative for estrogen and progesterone receptors. The majority of glioma cases were negative for estrogen receptors while strong progesterone receptor nuclear immunopositivity was observed in 59% of glioblastomas, 45% of anaplastic astrocytomas and 8% of low-grade astrocytomas (14). On the other hand, the antiestrogen tamoxifen has been found to be effective in decreasing glioblastoma cell proliferation (15). Thus, the expression of estrogen receptor in U138MG glioblastoma cells was successfully demonstrated (16). These findings might raise the question of whether the mechanism underlying this effect of tamoxifen works through the estrogen receptors of astrocytes. A recent study showed that an estrogen receptor-related antigen (ER-D5) was observed in the microvascular endothelial proliferations and in tumor blood vessels, suggesting its participation in the growth of the gliomas and tumor angiogenesis (17). Tamoxifen probably decreases cell proliferation through its effect on this antigen. We studied estrogen and progesterone receptors on both pathologic slides of our patient. However, neither estrogen nor progesterone receptor immunoreactivity were positive in glioblastoma multiforme, whereas the breast cancer cells were positive

only for progesterone receptors. She still uses tamoxifen predominantly for her breast cancer and no recurrence has been detected at either site to date.

The immunonegativity for p53 and c-erbB-2 oncogenes in both primary tumors may correlate with a better prognosis (8,9). Nevertheless, glioblastoma seems to be the major determinant of the survival time in this patient. The absence of estrogen receptor immunopositivity appears to limit the possible benefits of tamoxifen on malignant astrocytes, but at the same time we may speculate that the regrowth of glioblastoma can be slowed down with a possible decrease in angiogenesis.

We failed to demonstrate a common hormonal or oncogenetic basis for the neoplastic growth of these 2 associate diverse primary malignancies in our patient. However, further investigations including mutational analysis in such patients with mutiple primary neoplasms may help us to explore the genetic and epigenetic factors influencing carcinogenesis.

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